BIETTI'S TAPETORETINAL DEGENERATION WITH MARGINAL CORNEAL DYSTROPHY: CRYSTALLINE RETINOPATHY*

BY *Robert B. Welch,* MD

IN 1937 BIETTI[1,2] PUBLISHED A DESCRIPTION OF THREE PATIENTS WHO HAD BOTH A tapetoretinal degeneration and a corneal involvement consisting of deposits in the superficial layers at the limbus. The tapetoretinal degeneration was manifest by choroidal sclerosis, sparkling yellowish-white spots somewhat reminiscent of punctata albescens and scattered conglomerations of retinal pigment. The corneal deposits had crystalline characteristics similar to those in the retina. Two of the patients were brothers, thus suggesting a familial and inherited disorder. In 1942 Bietti[3] differentiated between the spots seen in his cases and those seen in retinitis punctata albescens and fundus albipunctatus. In 1951 Evans[4] reported "five cases of familial retinal abiotrophy." He described crystalline retinal degeneration but there is little detail recorded in his reports and no mention of corneal involvement. Lijó Pavîa[5] in 1953 reported four cases of "a rare form of luminescent crystalline tapetoretinal degeneration" but these cases bear little resemblance to those of Bietti. In 1968 Bagolini and Ioli-Spada[6] reported the follow-up on two of Bietti's original patients (the brothers) and six additional patients with a similar clinical picture. Two of the additional patients were also brothers.

It is the purpose of this report to present two cases of this unusual entity which were interestingly enough observed in Orientals. One patient was a 30-year-old Chinese woman and the other a 24-year-old Japanese man. I have added the term crystalline retinopathy as a subtitle to the designation given to this disease by Bagolini and Ioli-Spada since I feel that it is important that the most salient feature of this disease be included in its reference in the literature.

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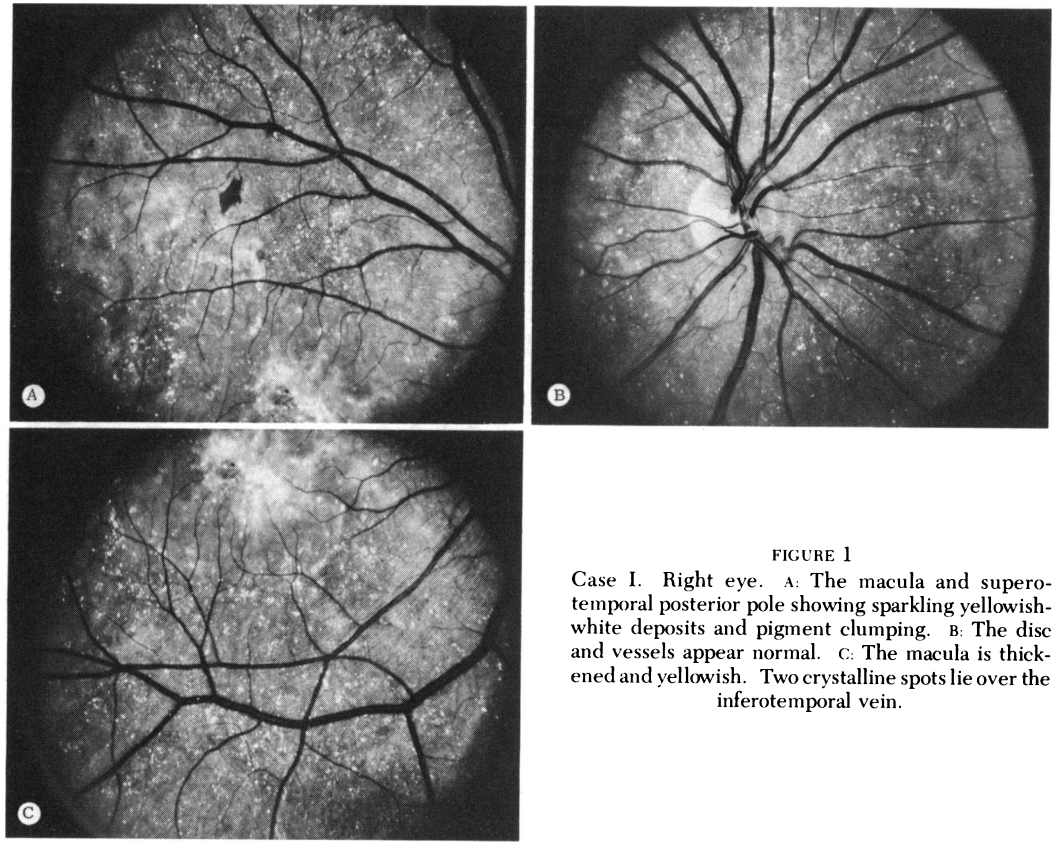

FIGURE 1

Case I. Right eye. A: The macula and superotemporal posterior pole showing sparkling yellowish-white deposits and pigment clumping. B: The disc and vessels appear normal. C: The macula is thickened and yellowish. Two crystalline spots lie over the inferotemporal vein.

CASE REPORTS

CASE 1

A 30-year-old Chinese woman presented to the Retina Clinic on July 15, 1975 complaining of decreased vision in both eyes for the past five months. The family history was negative for eye disease. Her parents, three sisters, and one brother had all been examined in Taiwan and reported as normal. The patient's past medical history was completely negative, except for (1) a cesarean section for the birth of her son 20 months previously, (2) a history of chronic skin disease diagnosed as psoriasis, and (3) a history of the use of birth control pills prior to January, 1975. Although the patient was a chemist, she did not believe she had been exposed to any toxic agents. The patient dated the onset of her difficulty to February 12, 1975 at 2:00 P.M. when while working in her chemical laboratory, she noted the numbers on her calculator were "jumping." The patient consulted her internist who found no abnormality on physical examination or laboratory studies. She was treated with vitamin B-12 for one month without benefit. Because of her problem she consulted several ophthalmologists, all of whom told her she had a degenerative disease of the retina of unknown etiology.

On examination, vision in the right eye was 10/200 and vision in the left eye 20/40. Ocular tensions were normal. Slit lamp examination was initially thought to be normal except for cells in the vitreous. Visual fields showed full peripheral fields with an incomplete ring scotoma in both eyes. The fundi were most remarkable (Fig. 1, 2). The disc and vessels appeared normal but there were many yellowish-white spots throughout the fundi with a crystalline appearance. These sparkling spots were primarily deep in the retina but all layers were involved and an occasional spot lay over a retinal vessel. The pigment epithelium showed atrophy with large choroidal vessels showing through. There were areas of large pigment-clumps in both fundi. The macula in the right eye was yellowish and appeared to be edematous. A review of the literature revealed the report by Bietti and when the patient returned for follow-up and photography, slit lamp examination demonstrated the fine crystalline deposits in the superficial layers of the cornea at the limbus (Fig. 3). These deposits were very fine and could be easily overlooked unless specifically searched for. Fluorescein angiography demonstrated widespread atrophy of the pigment epithelium as well as some areas of choriocapillaris loss around the optic nerve and in the macular area (Fig. 4). There was diffuse pigment abnormality throughout the posterior pole and in the equatorial area. The patient returned to Taiwan in November, 1975 and was hospitalized for study and treatment. She received six doses of typhoid vaccine over a twenty-three day period and on discharge her vision was reported to have improved. The patient returned to the United States and was seen again on February 14, 1976. Vision in the right eye was 20/70 and vision in the left eye was 20/30. The ophthalmoscopic appearance was unchanged except the right macula appeared less elevated than on previous examination. The patient was admitted to The Wilmer Institute on May 4, 1976 and a corneal and conjunctival biopsy performed on the right eye and submitted to the Eye Pathology Labora-

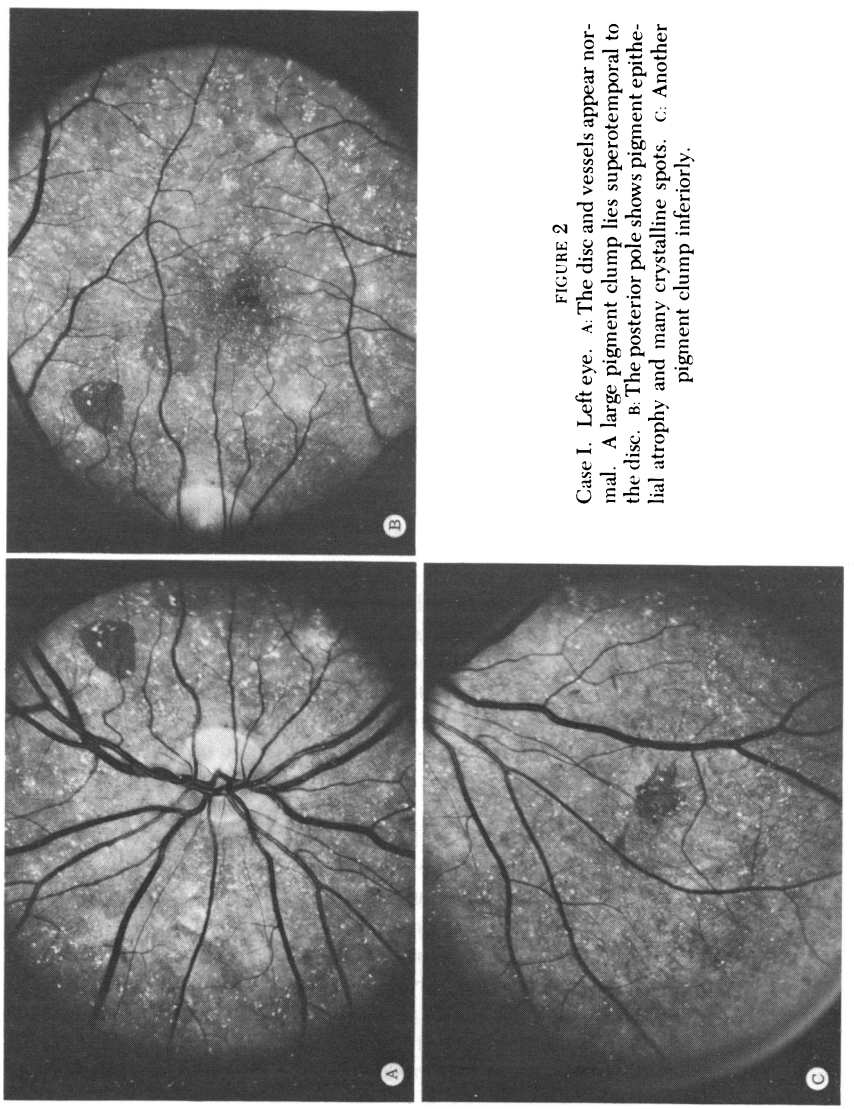

FIGURE 2

Case I. Left eye. A: The disc and vessels appear normal. A large pigment clump lies superotemporal to the disc. B: The posterior pole shows pigment epithelial atrophy and many crystalline spots. C: Another pigment clump inferiorly.

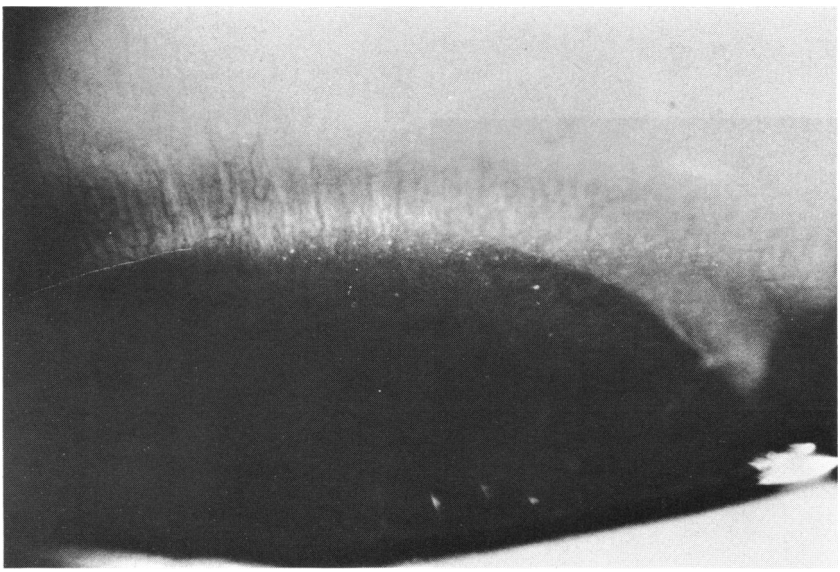

FIGURE 3
Case I. Superior limbus of the right eye showing fine crystalline deposits in the superficial layers.

tory. No crystalline material was found, but a positive reaction was obtained with the oil red 0 stain within the fibroblasts of the conjunctival substantia propria (Fig. 5). Electron microscopic studies disclosed inclusion bodies within the fibroblasts of both cornea and conjunctiva and rarely in the corneal epithelial cells (Fig. 6). These inclusions were characteristic of lipid. While in the hospital, a skin biopsy was performed and reported to be diagnostic of psoriasis. Amino acid studies on the serum and urine were unremarkable except for an unknown slow-moving compound in the urine. Metabolic urinalysis was negative. A routine laboratory survey was normal. Lipid and lipoprotein analysis revealed no abnormalities. The ERG and EOG were both abnormal (Fig. 7). The light peak to dark trough ratio of the EOG was 1.00 for the right eye and 1.06 for the left eye. The scotopic ERG was slightly reduced and the photopic ERG was 35% of normal. The patient was discharged on May 13, 1976 and has been closely observed. In June, 1976 she developed cervical herpes zoster which cleared within a short time. On March 16, 1977 vision in the right eye was 20/40 -3 and vision in the left eye 20/30. Visual fields were unchanged and fundus appearance the same. The corneal crystals were still present at the limbus. Examination of the patient's three year old son revealed no abnormalities.

CASE 2

The second case of this syndrome strangely enough was seen within a few weeks of the first case. The fundus photographs from a 24-year-old Japanese man were

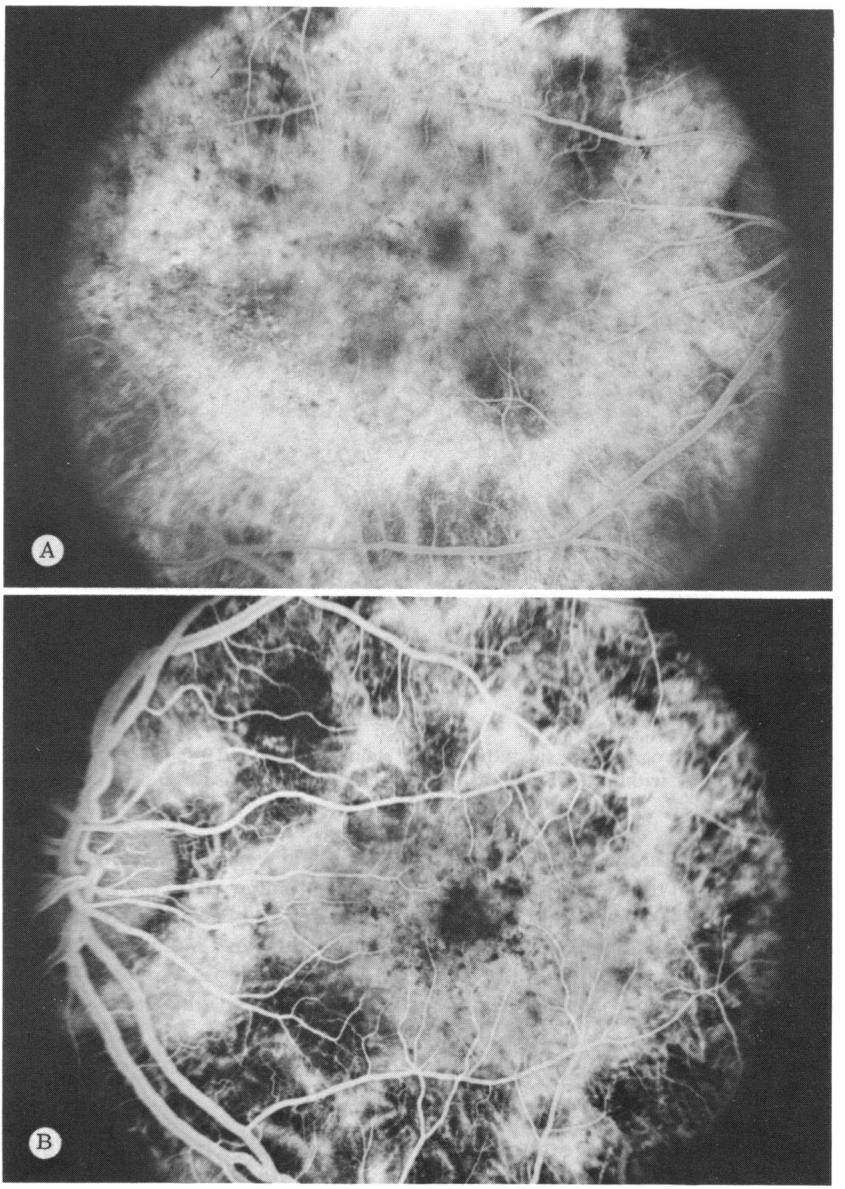

FIGURE 4

Case I. Fluorescein angiograms. A: The right fundus shows marked atrophy of the pigment epithlium with areas of disappearance of the choriocapillaris. B: The left fundus shows a similar picture. Note pigment aggregation temporal to the disc.

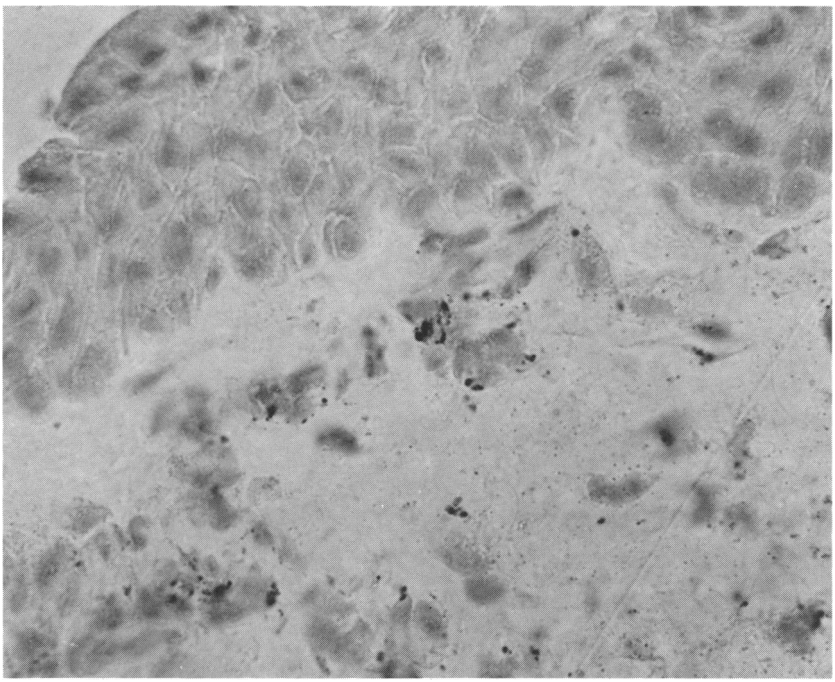

FIGURE 5
Case I. Photomicrograph of conjunctival biopsy stained with oil red 0 showing lipid material within the fibroblasts of the substantia propria × 800.

presented to me at the Walter Reed Army Hospital in August, 1975 and appeared almost identical to my recent case (Fig. 8). In September, 1975 the patient who was a young Marine being evaluated at the Bethesda Naval Hospital, was examined. This patient had 20/15 vision in each eye and minimal symptoms. Studies performed at Bethesda, including a corneal biopsy, are said to have been negative. There was no family history of any similar difficulty.

DISCUSSION

From a review of the literature and the cases presented here, we may make the following observations about this disease entity:

RETINAL INVOLVEMENT

The most striking part of this disease is the retinal change which consists of yellowish-white spots that reflect light like crystals and appear at all

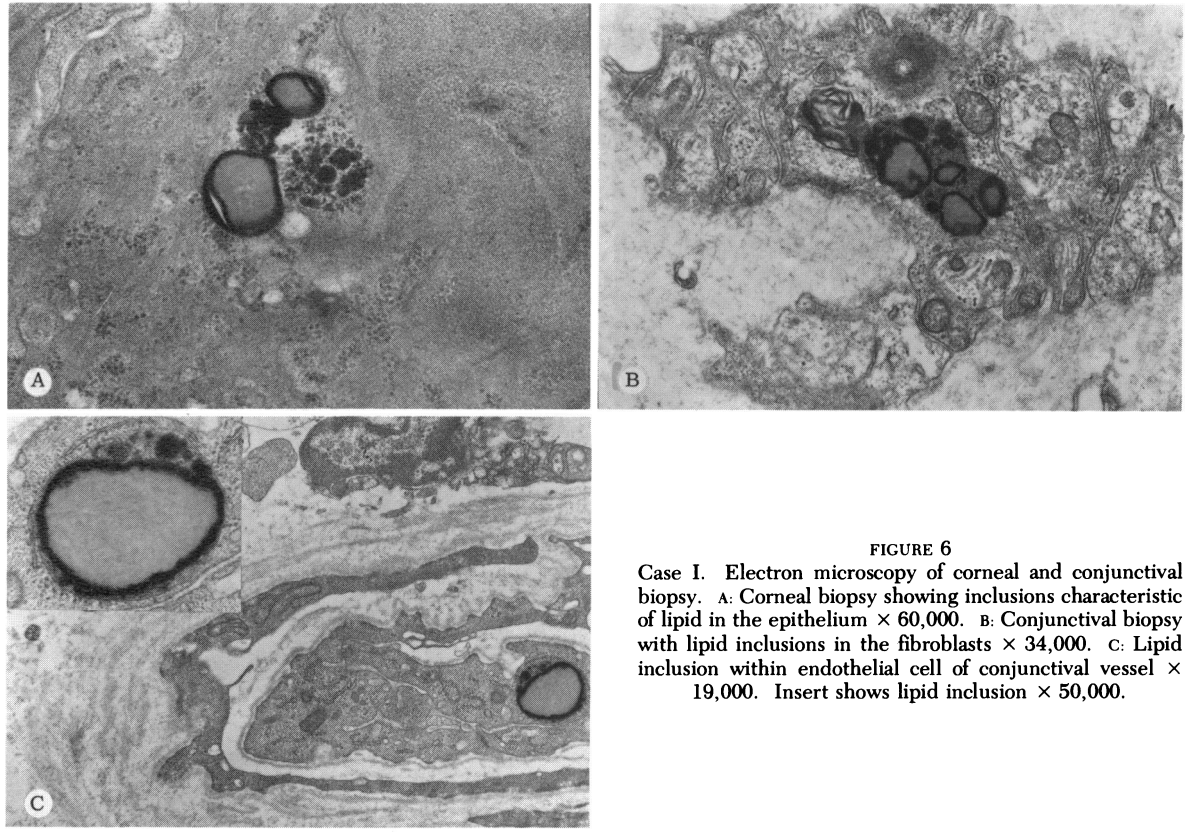

FIGURE 6

Case I. Electron microscopy of corneal and conjunctival biopsy. A: Corneal biopsy showing inclusions characteristic of lipid in the epithelium × 60,000. B: Conjunctival biopsy with lipid inclusions in the fibroblasts × 34,000. C: Lipid inclusion within endothelial cell of conjunctival vessel × 19,000. Insert shows lipid inclusion × 50,000.

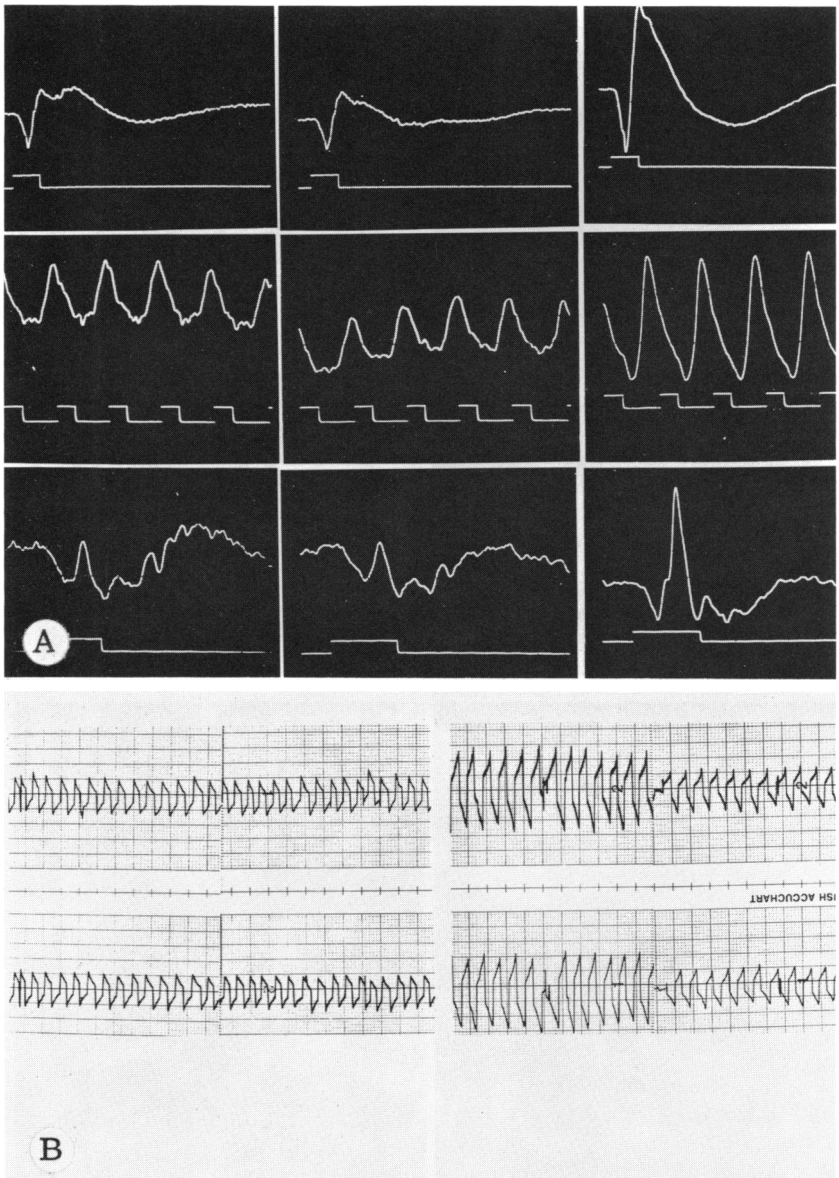

FIGURE 7

A: Electroretinogram of Case I. Upper tracings are scotopic, middle are flicker and lower are photopic responses. Left and middle columns are the right and left eye of the patient while the right column shows the tracings from a normal individual. B: Electro-oculogram of Case I. The left tracings are from the right and left eyes of the patient while the right tracings are from a normal individual.

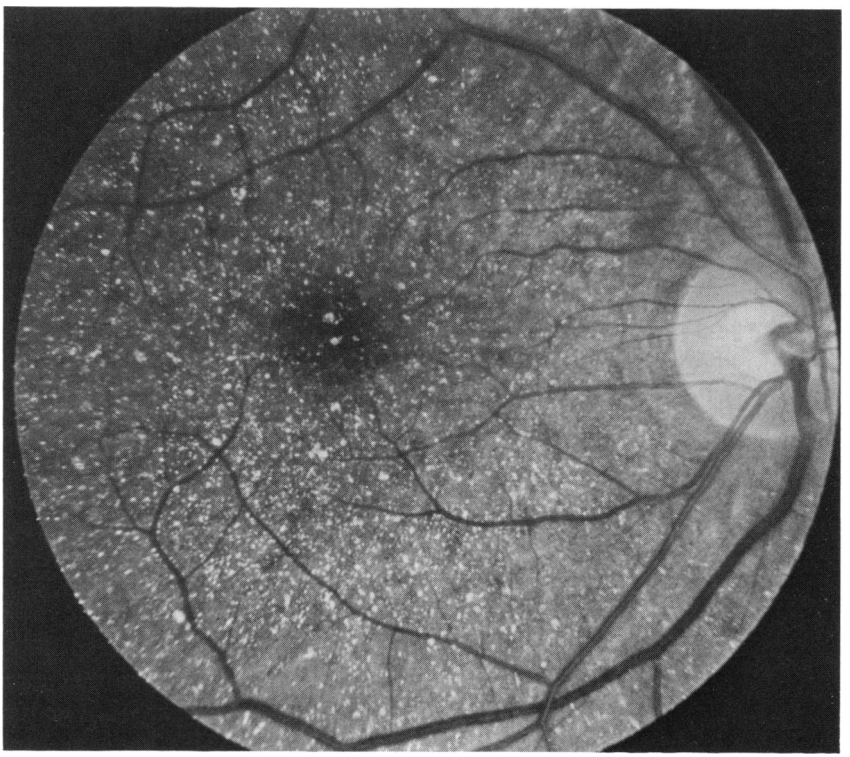

FIGURE 8
Case II. Left eye. The fundus shows crystalline spots similar to those observed in Case I.

levels of the retina, primarily deep but also superficial to retinal vessels. The optic nerve and vessels are normal in early cases. The disease has not been observed in childhood and does not become symptomatic until the individual is in his 20's or 30's. There is pigment epithelial atrophy and loss of the choriocapillaris and large clumps of pigment are frequently seen throughout the posterior pole. Although the present cases showed no family history, the presence of the disease in two sets of brothers described in the literature alerts one to the possibility of an hereditary disease.

CORNEAL INVOLVEMENT

The yellowish-white crystalline deposits at the limbus are easily overlooked. They appear most marked at the superior and inferior limbus with very few seen at the nasal and temporal limbus. They appear to be in the epithelium and superficial layers of the corneal stroma and may occasionally be seen in the conjunctival epithelium near the limbus.

PATHOLOGY

Biopsy attempts made in the past to ascertain the nature of the corneal deposits have been unsuccessful. In the present report (Case I) material from the corneal limbus and conjunctiva was studied extensively. In spite of the clinical appearance of crystals in the tissue, the pathologic specimens revealed lipid by the oil red 0 stain and electron microscopy studies.

CLINICAL COURSE

From Bagolini and Ioli-Spada's report, it is apparent that these patients may develop marked visual loss. The improvement of vision in the first patient following typhoid therapy is unexplained but documented.

COMMENT

This disease entity appears to be a tapetoretinal degeneration and the involvement of the cornea by an apparent lipid material would point to a metabolic disorder. The ophthalmoscopic picture and corneal findings are quite characteristic and I feel represent a distinct entity rather than a form of retinitis punctata albescens occurring with the anomalous condition of marginal corneal dystrophy as suggested by some authors.[7,8] However, it would be of value to examine patients with typical retinitis punctata albescens carefully at the slit lamp since corneal deposits may be easily overlooked. It is hoped that this report will provide a stimulus to accumulate cases of this type and perhaps identify the basic problem.

SUMMARY

In 1937 Bietti reported a tapetoretinal degeneration with associated corneal deposits at the limbus. The hallmark of the disease was the crystalline characteristics of the retinal spots as well as those at the corneal limbus. Bagolini and Ioli-Spade in 1968 presented a 30 year follow-up on Bietti's cases and presented six additional cases. The present report deals with this entity in Orientals, a Chinese woman and a Japanese man. Corneal and conjunctival biopsy from the female patient revealed a lipid deposition in both fibroblasts and epithelium. The term "crystalline retinopathy" has been added to the description of this entity since it defines the most characteristic feature of the syndrome.

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DISCUSSION

DR BANKS ANDERSON, JR. Dr Welch has described two patients who seem to have Bietti's tapetoretinal degeneration with corneal dystrophy. Few of us have recognized cases of this type and their rarity has cast some doubt upon the existence of the condition as a separate disease entity. The late Alex Krill, for example, hypothesized that Bietti's cases represented an adult form of cystinosis (*Hereditary Retinal and Choroidal Diseases*, 1977, p 749) while Duke-Elder and Francois have considered the condition a variant of fundus albipunctatus.

If the condition is in fact more than a fortuitous association of two separate entities affecting the retina and cornea, a genetic or aquired metabolic abnormality seems the most likely cause. The crystalline nature of the deposits which Dr Welch has emphasized, suggests a storage disease. Although his attempts to characterize the crystalline material by studies of the conjunctival and corneal epithelium were unsuccessful, one can readily think of examples of storage diseases, such as the Fanconi syndrome, where crystals may be found in both the cornea and retina. Bullock and Albert have recently brought to our attention another interesting storage disease which may be related to these cases. They have reported a patient in whom calcium oxalate crystals were found in the retina following prolonged methoxyflurane anesthesia. Although corneal changes were not noted, the pictures and description of the yellowish-white retinal deposits seem similar to those of the cases reported by Dr Welch today. Although oxalosis has also been seen following ingestion of ethylene glycol antifreeze and in rhubarb gluttony, retinal crystals have as yet not been described in oxalosis from these sources. It is interesting however that transient nystagmus has been observed in a group of women exposed to heated ethylene glycol (Troisi FM, *Br J Ind Med* 7:65, 1950). Could the "jumping" of the eyes noted by the first patient (Case 1) while working in her chemical laboratory have been associated with exposure to ethylene glycol vapor? Could the anesthetic used during her cesarean section

have been methoxyflurane? If either were the case oxalosis might be considered in the differential diagnosis. I wonder, Dr Welch, if you have further information on these points?

Dr Welch's stress on the crystalline nature of the retinal deposits also brings to mind a patient of mine with crystalline retinopathy associated with calcific aortic stenosis which is illustrated in these slides. The crystals that you see here are probably intravascular but in most cases the vessels are too small to be visible ophthalmoscopically.

The family histories of the patients reported by Dr Welch were negative while Bietti's original patients were brothers. Bagolini and Ioli-Spada in their article reported a second pair of brothers. Although this familial pattern might imply a recessive or sex-linked inheritance, aquired disease can not be ruled out. Dr Welch's cases also differ from those described by Bietti and others in that progressive deterioration of visual function has to date not been documented. Indeed, the vision in the first patient has actually improved during the follow-up period. This improvement also suggests the possibility of aquired disease. If on the other hand, the progressive nature of the disease becomes established in these patients with further follow-up, the unique nature of the disease described by Bietti will have further confirmation.

It is obvious from this report that those of us interested in flecked and spotted retinas will have to spend more time looking at the corneas of our patients. I suspect that if we do, we may discover other patients with the interesting association of corneal and retinal deposits pointed out to us today. I should like to thank Dr Welch for sending me his manuscript well in advance of the meeting and the program committee for the privilege of discussing this interesting paper.

Professor Jules François. I was very much interested in Doctor Welch's presentation. We had the opportunity to observe two cases identical to those described by Doctor Welch, with the exception of the corneal crystals, which we could not find. One patient came from Quatar and his brother was also affected. The other patient came from Algeria. Moreover, I know of five cases from Brasil, so that all together, more or less, twenty cases are known: six of them belong to three sibships and the parents of our sibships (two brothers) were consanguineous. An autosomal recessive inheritance can thus be accepted. Although an error of metabolism seems to be the cause, all the examinations along that line were negative. In our two cases, cystinosis and CA oxalosis could be excluded.

Dr J. Donald M. Gass. I would like to present two patients who further illustrate the interesting disease presented by Doctor Welch. The first patient is a 54-year-old white man who recently became aware of paracentral scotomas. He had 20/20 vision in both eyes and widespread areas of geographic atrophy of the pigment epithelium throughout the fundus. He had visual field defects that corresponded with these areas of depigmentation of the pigment epithelium. Many fine dot-like crystalline opacities were present at the level of the pigment epithelium. They were concentrated in the areas of relatively normal appearing

pigment epithelium. His electroretinographic findings were slightly abnormal. His electro-oculogram was normal. His past medical history was unremarkable. He had normal levels of serum ornithine and urine oxylates. There was no family history of this disease. Fluorescein angiography demonstrated atrophy of the choriocapillaris confined to the areas of geographic atrophy of the pigment epithelium. We examined this patient very carefully on several occasions and have been unable to detect any evidence of corneal crystals.

The second patient is a 43-year-old Chinese woman, who gave a history of mild nyctalopia for twelve years and gradual decreasing visual fields for three years. She was also aware of defective color vision. Visual acuity in the right eye was 20/40 and in the left eye was 20/25. The family history that included three brothers and two sisters was negative. There was no other family history of eye disease or consanguinity. The ophthalmoscopic and fluorescein angiographic findings were identical to that in the previous case. The field examination revealed dense scotomas corresponding to the areas of atrophy of the retinal pigment epithelium. She had minimal rod and cone response on electroretinography. Her electro-oculogram was abnormal. I have not examined this patient but her referring physician did not note the presence of corneal crystals.

I wish to illustrate three other diseases characterized by the presence of crystals within the retina or pigment epithelium. The first case is an example of oxalosis secondary to methoxyflurane anesthesia. This case was previously reported by Doctor Bullock and Doctor Albert (*Arch Ophthalmol* 93:26-30, 1975). Ophthalmoscopically and histopathologically, these patients have multiple oxalate crystals deposited in the retina and pigment epithelium. This patient developed renal failure and died following complication of immunosuppressant therapy following renal transplantation. Histopathologic examination of the kidneys revealed extensive oxalate deposits. This next patient illustrates multiple crystalline deposits in the retina of a 31-year-old black man with mental and motor retardation, ichthyosis, generalized weakness, and spasticity related to the Sjogren-Larsson syndrome (*Arch Ophthalmol* 80:308-316, 1968). The last case of Doctor David Donaldson is a patient with cystinosis and multiple cystine crystals throughout the fundus of both eyes. Histopathologically, these crystals are deposited primarily in the choroid.

Dr David Cogan. I had the opportunity of examing Doctor Welch's patient who was then at the National Naval center in Bethesda. The question was whether these deposits could be oxalate crystals. This possibility was appealing because oxalate crystals do occur at the level of the rods and cones or in the pigment epithelium under specific, however, rare, conditions. Thus, they may ocur in the outer portion of a detached retina of long standing (*Arch Ophtahlmol* 60:366-371, 1958) or they may occur in the epithelium with certain types of systemic oxalosis (*Invest Ophthalmol* 13:256-265, 1974). Yet, neither of these conditions applied, as Doctor Welch pointed out, to the present patient.

I would also like to comment on the lipid bodies which Doctor Welch demonstrated in the specimen from the conjunctival biopsy. These seem to be to be

typical lipofuscin bodies. I doubt they could be responsible for the reflectile particles seen ophthalmoscopically in this patient since lipofuscin is normally present, and often abundant, in the pigment epithelium and has none of the characteristics shown in this patient's fundus.

DR CLEMENT MCCULLOCH. Mr President, I am moved to discuss Dr Welch's excellent paper because of an interest in a case of what we have been calling Snyder's corneal dystrophy. The patient is a young Chinese man of about 30 years. He has very milky appearing corneas with an outer arcus at the limbus and an inner arcus closer to the center of the cornea. In each cornea he had approximately three areas of crystals, these crystals having a rather feathery appearance. I could not see any crystals in the fundi, although his corneas are cloudy enough that fine crystals may not be visible. Electroretinograms are normal. His visual acuity is 20/40 in each eye.

The general medical workup is negative. His blood cholesterol, triglycerides and lipid electrophoresis are normal. Tests for lecithin-cholesterol acyltransferase deficiency are negative.

Biopsies of his corneas in the areas of the crystals show deposits of fat, particularly in Bowman's layer. In the stroma the fatty material is less, but present. In the epithelium are a number of macrophages which contain fat and which seem to be in the process of being extruded. There are no clefts that looked like they would represent crystals. Three biopsies were taken in an endeavour to find these clefts, but none was seen. In the areas where the crystals are clinically present there are aggregates of fat just deep to Bowman's membrane, and I wonder if the clinical appearance is not due to those aggregates. Following Dr Welch's advice I will go back and look more carefully for crystals in the fundus. His point is well made. If one sees crystals in the fundus, look carefully in the cornea. Also; I would feel if one sees crystals in the cornea, look carefully in the fundus.

DR ROBERT B. WELCH. I would like to thank all the discussants for their very interesting comments — Dr Anderson, Dr Francois, Dr Gass, Dr Cogan, and Dr McCulloch.

In answer to Dr Anderson, I was alert to all those exotic things that cause crystals. She had had a cesarean section twenty months previously, but had not had penethrane anesthesia. We thought of cystinosis but there was no evidence of this. It was February when she noted her problem but there was no history of antifreeze ingestion. She was too young for calcific stenosis. I even asked her if she had been eating rhubarb but she admitted only to an occasional Gensing root.

I thought Dr Francois' cases were indeed interesting. As far as consanguinity is concerned this was not present here as her father was from Mongolia and her mother from Shanghai.

Dr Gass' cases are particularly interesting because the symptoms appeared so late, one at age 54 and one at age 47. The fluorescein pictures certainly show the marked loss of choriocapillaris as in my cases.

I enjoyed Dr Cogan's comments. When I performed the corneal biopsy and sent the specimen to Dr Dick Green, I asked him what kind of crystals these were. When he told me these were lipid deposits I was amazed for I was unaware that lipid could take on a crystalline characteristic.

Dr McCulloch's comments on Snyder's corneal dystrophy are especially valuable since they support the fact that lipid may assume a crystalline form.

Thank you very much.